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GUIDE

Using Real-World Data and Real-World Evidence to Support Rare Disease Programs

A key challenge of developing therapies for rare diseases is the availability of relevant data. With small, often geographically-dispersed patient populations, natural history information is typically sparse or even unknown. Without this data, it may be difficult to identify biomarkers for measuring drug activity or to define clinical trial endpoints or outcome measurements. Consequently, sponsors may need to look beyond traditional randomized clinical trials to support their development programs. In recent years, the FDA and EMA have begun to embrace the concept of using real-world data (RWD) or real-world evidence (RWE) to bridge knowledge gaps in rare disease research and development. For instance, if including a placebo arm is deemed unethical, a sponsor may be able to use RWD and RWE as a control or a comparator.

In this guide, we explore how RWD and RWE can be leveraged to address data challenges and support regulatory decision-making for rare diseases.

Defining rare diseases

In the US, a rare disease is defined as a one that affects fewer than 200,000 people.[1] The European Medicines Agency (EMA) considers a disease to be rare if it affects less than one in 2000 citizens, which is the equivalent of fewer than 250,000 people in the EU.[2] Despite these stringent definitions, over 7,000 rare diseases are recognized worldwide, affecting 400 million people, and approximately 250 new rare diseases are identified each year. Half of people affected by these conditions are children, and, to date, 95% of all rare diseases do not have a single FDA-approved drug treatment.[3]

Distinguishing between RWD and RWE

While the terms RWD and RWE are often used synonymously, they are distinct from a regulatory perspective:[4]

- RWD is data relating to patient health status and/or health care delivery that is routinely collected from a variety of sources, including consumer wearable devices (see Figure 1).
- RWE is derived from the analysis of RWD and provides clinical evidence regarding the usage and potential benefits or risks of a medical product, which can be used to inform regulatory decision-making, reimbursement policies, or clinical guidelines. Often, the process of generating RWE involves integrating data from various sources to create usable, structured datasets that can be analyzed and presented in a format that is acceptable to regulatory agencies or other stakeholders.

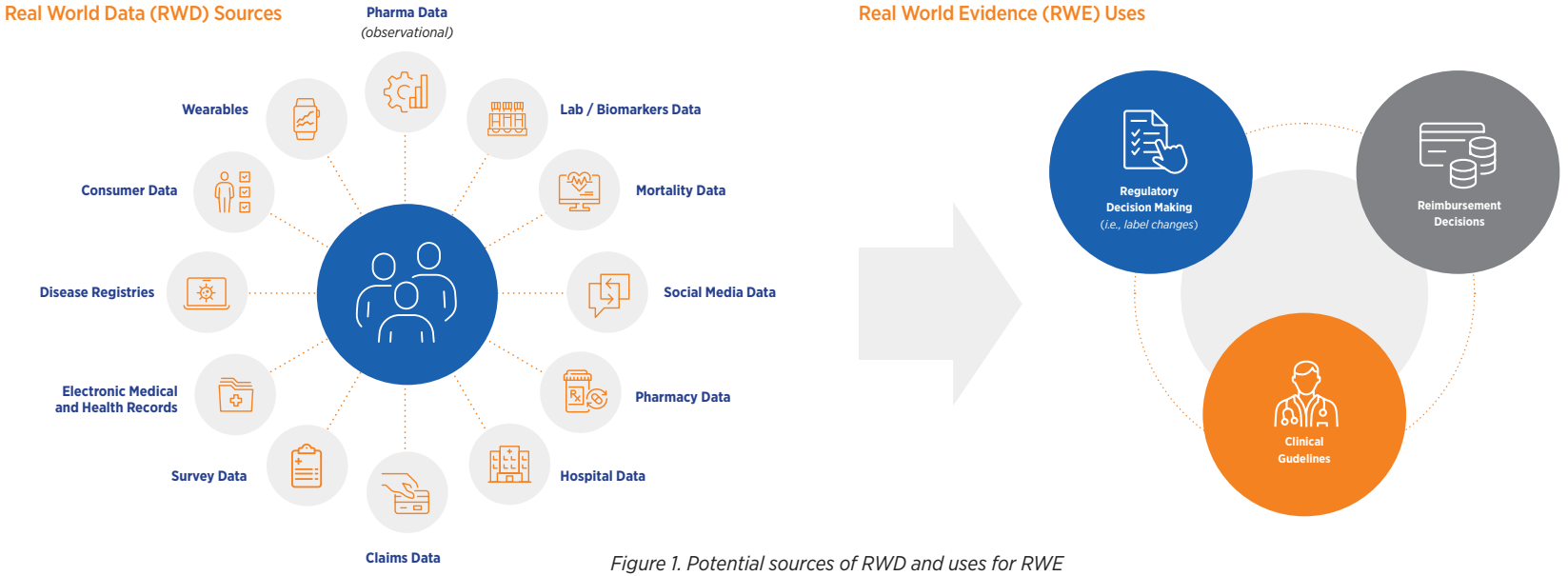


Figure 1. Potential sources of RWD and uses for RWE

Understanding the regulatory framework

The regulatory framework for RWD and RWE is continually evolving. Pursuant to provisions of the 21st Century Cures Act, which was signed into law on December 13, 2016, the FDA created a framework for evaluating the potential use of RWE to help support approval of a new indication of a drug or to help satisfy post-approval study requirements.[5] Since 2017, the FDA has released seven guidance documents on the use of RWD and RWE to support regulatory decision-making:[4]

1. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
2. Use of Electronic Health Records in Clinical Investigations
3. Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics
4. Data Standards for Drug and Biological Product Submissions Containing Real-World Data
5. Considerations for Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
6. Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
7. Assessing Electronic Health Records and Medical Claims to Support Regulatory Decision-Making for Drug and Biological Products

Given the FDA's willingness to consider the inclusion of RWD and RWE in regulatory submissions, sponsors will find it worthwhile to begin a dialogue with the agency during the early stages of development.

Addressing challenges of using RWD and RWE in rare disease programs

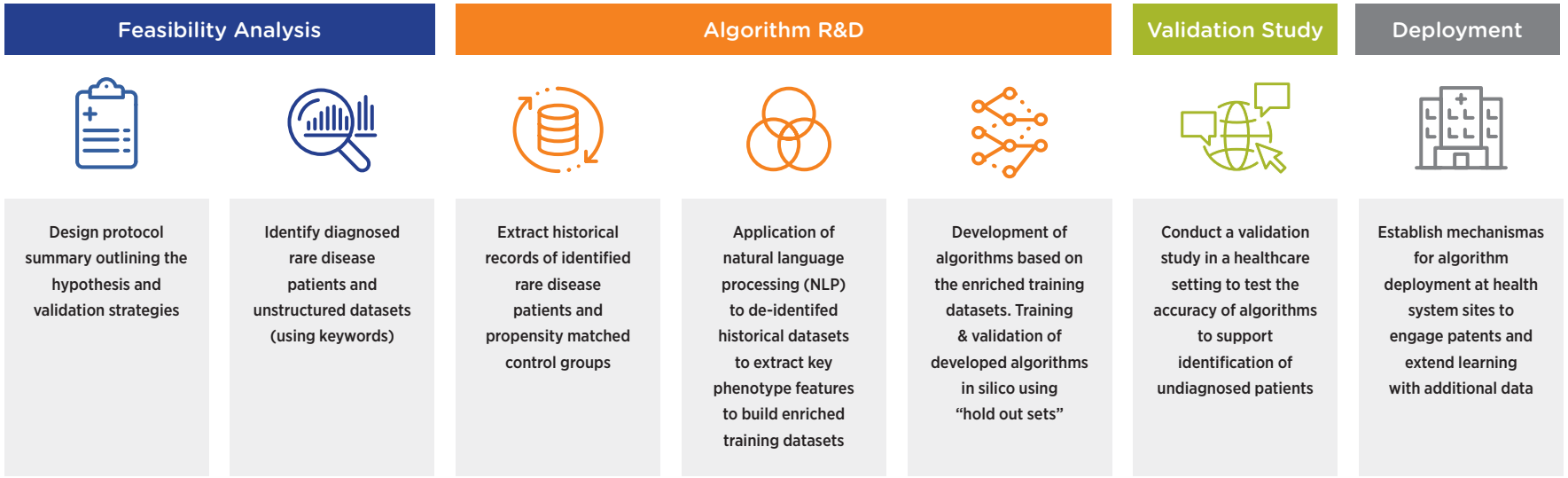
Sponsors often encounter the following common challenges with rare disease data:

- Natural history is poorly understood, and knowledge of the pathophysiology and clinical manifestations of the disease is incomplete or absent.
- Well-characterized efficacy endpoints appropriate for the disease are not available.
- The disease is under-represented, incorrectly characterized, or not captured in health care coding systems due to its rarity.

With increasing globalization and connectivity, sponsors now have greater opportunity to identify rare disease patients across geographies through RWD. To develop a deep understanding of a rare disease, it is necessary to look at patients' longitudinal data across various sources, including electronic health records, laboratory reports, genomics databases, and pharmacy data. Even if all this unstructured RWD is available, there is still a need to integrate and harmonize it and then link it to clinical trial data.

The concepts of tokenization and aggregation of RWD, which have long been used in other Big Data applications, have started to gain a foothold within the clinical research environment. Tokenization is the process of replacing sensitive data with non-sensitive unique identification symbols called tokens, while aggregation is the process of gathering and organizing raw data. Using these concepts, unstructured data from multiple sources can be tagged with a unique identifier that can then be linked to a patient's clinical trial data. That unique identifier enables researchers and sponsors to capture longitudinal data that can be converted into a structured dataset, which can then be analyzed to generate RWE to support study-related or regulatory decision-making.

Figure 2. Sample process for using RWD to identify undiagnosed rare disease patients



Utilizing RWD and RWE in rare disease research

Potential applications of RWD in rare disease programs include:

- Developing a deeper understanding of the disease of interest
- Finding patients who may be eligible to participate in a planned clinical study
- Detecting the disease in undiagnosed patients
- Serving as synthetic control arms

Successfully utilizing RWD to support regulatory decision-making requires a disciplined process of feasibility analysis, algorithmic research and development, validation, and deployment (see Figure 2).

Preparing to meet with the FDA

Sponsors may benefit from engaging with the FDA early to discuss plans for including RWD or RWE in their development programs. A pre-IND or Type C meeting can be used to discuss regulatory expectations regarding study design, conduct, and analysis. To prepare for this meeting, sponsors should:

- Provide the draft protocol and statistical analysis plan (SAP) for review to garner feedback from the agency and avoid bias
- Outline the suitability of the data source(s) for addressing the key research question(s) and provide justification supporting the selection of the proposed data source(s)
- Demonstrate how data integrity is maintained, from data extraction, curation, and transformation to reporting of results
- Clarify the intended role of RWD and RWE in contributing to, or augmenting, the totality of evidence proposal

Conclusion

Sponsors are increasingly interested in harnessing insights from RWD and RWE to support drug development programs, especially for rare and ultra-rare diseases. Understanding what regulators expect to see and how to generate clinically meaningful data that meets study data standards is critical for successful inclusion of RWD and RWE in regulatory submissions. At Premier Consulting, we have experience in liaising with the FDA to leverage RWD and RWE in support of rare disease programs. To learn more about how Premier Consulting can help move your product development strategy forward, contact us.

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[1] *U.S. Food and Drug Administration. Rare Disease at FDA. Available at* https://www.fda.gov/patients/rare-diseases-fda.

[2] *Eurordis. What is a rare disease? Available at* https://www.eurordis.org/information-support/what-is-a-rare-disease/.

[3] *Global Genes. RARE Disease Facts. Available at* https://globalgenes.org/rare-disease-facts/.

[4] *U.S. Food and Drug Administration. Real-World Evidence. Available at* https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.

[5] *U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program, December 2018. Available at* https://www.fda.gov/media/120060/download.

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Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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